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09/630,215	08/01/2000	John F. O'Connor	54205-A-PCT-US/JPW/SHS/MV	7218

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 05/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/630,215	O CONNOR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,14,15,18,20,21,27,28,31,32,34, 38,39,42-44,46,49,51 and 56* is/are pending in the application.

4a) Of the above claim(s) *44,46,49 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8,14,15,18,20,21,27,28,31,32,34, 38,39 and 42* is/are rejected.

7)☒ Claim(s) *43* is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1-3,6,8,14,15,18,20,21,27,28,31,32,34, 38,39,42-44,46,49,51 and 56.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group 1, claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 38-39, and 42-43, with traverse, filed 2/11/02 in Paper No. 10 is acknowledged and has been entered. Claims 44, 46, 49, 51, and 56 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention.

2. Applicant's traversal of the restriction requirement set forth in Paper No. 8* is acknowledged. The traversal is on the basis that the claims in Group 1 are not independent from the claims in Group II and III and do not define patentably distinct inventions because all three groups are related to the same antibody having "related use" for all three groups. Applicant argues that the claims define a single inventive concept; thus, a single inventive effort, and thus the search and examination does not pose serious burden to the Examiner.

Applicant's argument is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate classification and search. Further, each independent and distinct invention is presented with related antibody having a separate "use"; thus requiring distinct functional requirements; thus, literature search for and examination of each of the methods, are distinct. While searches would be expected to overlap, there

is no reason to expect the searches to be coextensive. Applicant's contention that search and examination of the entire application can be made without serious burden to the Examiner, even if it includes independent and distinct inventions, therefore, is without merit.

Restriction does not prevent Applicant from presenting any number of claims covering numerous statutory classes if they choose. Instead, restriction merely permits the Office to limit its examination to one independent and distinct claimed invention per application.

The record set forth in the previous restriction requirement clearly indicated that the delineated inventions are in fact patentably distinct each from the other or independent from the other.

Therefore, the requirement is deemed proper and is therefore made FINAL.

Accordingly, claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 38-39, 42-44, 46, 49, 51, and 56 are pending. Claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 38-39, and 42-43 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 39, and 42-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete for omitting essential elements and method steps, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, it is unclear how the "measuring" step is performed in the absence of a label for detection.

Claim 1, step c) has improper antecedent basis problem in reciting "the amount of EPAMI HcG ... from a temporally matched normal pregnant subject." Change to --an amount of EPAMI HcG ... -- for proper antecedent basis.

Claim 1, step c) is indefinite in reciting "relative absence" in step c) because the term "relative" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Regarding claim 2, step b), the term "any" renders the claim indefinite because the claim includes elements not clearly disclosed (those encompassed by "any complex"), thereby rendering the scope of the claim unascertainable.

Claim 2, step b) lacks clear antecedent support in reciting, "the hCG isoform".

Claim 2, step b) is confusing in reciting, "binding to the complex the capture antibody and the hCG isoform". Does Applicant intend "binding the complex formed in step a) between the capture antibody and the EPAMI-hCG". Further, it is unclear which component in the complex of step a) the detection antibody binds since the complex comprises the capture antibody and the EPAMI-hCG.

Claim 2, step d) has improper antecedent basis problem in reciting "the amount determined for a normal pregnant subject." Change to --an amount determined ... -- for proper antecedent basis.

Claim 2 is indefinite in reciting "relative absence" in step d) because the term "relative" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 3 lacks clear antecedent support in reciting, "said antibody" and "the antibody" because a capture antibody and a detection antibody have been previously recited in this instant claim and claim 1 from which it depends.

The term " substantially " in claim 3 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 6 is incomplete for omitting essential elements and method steps, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, it is unclear how the "measuring" step in step b) is performed in the absence of a label for detection.

Claim 6, step c) lacks clear antecedent support in reciting, "said antibody" and "the antibody" because it is unclear which previously recited antibody is being referred back to for antecedence.

Claim 6 is incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural

connections. See MPEP § 2172.01. Specifically, claim 6 fails to clearly define the relationship between each of the recited components, i.e. EPAMI-hCG, intact non-nicked hCG, from here on, INN-hCG, each of the first and second "capture" antibodies, and the "second" detection antibody. Claim 6, step c) is confusing because as recited, it is unclear which component between EPAMI-hCG and INN-hCG binds and forms a complex with which antibodies and whether one or more complexes are being formed. Please clarify.

Claim 6, step c) lacks antecedent support in reciting, "with the amount determined".

Claim 6, step c) is vague and indefinite in reciting, "a second detection antibody" because there appears to be no recitation of "a first detection antibody". Further, it is unclear what component the detection antibody intends to "label and detect".

The terms "high" and "low" in claim 6, step c) are relative terms which render the claim indefinite. The terms "high" and "low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 8 is indefinite in reciting "similar" because the term "similar" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 8 is confusing in reciting, "amounts of early pregnancy associated molecular isoform of hCG in the sample similar to amounts of early pregnancy

associated molecular isoform of hCG" because it is unclear what Applicant intends to encompass by such recitation. Please clarify.

Claim 14, step a) in vague and indefinite in reciting, "contacting a capturing antibody ... with a solid matrix ...under conditions permitting binding of the antibody with the solid matrix" because as recited, it appears that an immunological binding interaction took place between the capturing antibody and the solid matrix which is not Applicant's intent. Perhaps, Applicant intends "immobilizing a capturing antibody ... into a solid matrix".

Claim 14, step b) lacks antecedent support in reciting, "the bound matrix". Perhaps, Applicant intends, "the solid matrix which has the capturing antibody immobilized thereto".

Claim 14, step c) lacks clear antecedent support in reciting, "the bound matrix".

Claim 14, step d) lacks clear antecedent support in reciting, "the separated bound matrix".

Claim 14, step d) is confusing because it is unclear what structural cooperative relationship exists between the recitation of "binding of antibody and antigen in the sample" and the EPAMI-hCG, capturing antibody, and detecting antibody recited in the previous steps. For clarity, it is suggested that Applicant uses consistent terminology in defining specific elements in the claims.

Claim 14, step e) lacks clear antecedent support in reciting, "the bound antibody on the bound matrix" because both capturing antibody and detecting antibody are bound to the matrix. It is suggested that consistent terminology be used to distinctly

define between elements in the claim. For example, the elements in the claim include: a capturing antibody immobilized into the solid matrix that binds EPAMI-hCG, the detecting antibody specific for or that binds hCG, etc. Further, it is unclear, as recited, what structural cooperative relationship exists between EPAMI-hCG and hCG in the claims.

Claim 14, step e) is indefinite in reciting "similar" and "less amount" because the terms "similar" and "less amount" are subjective terms that lack a comparative basis for defining their metes and bounds.

Claim 15, step a) is ambiguous in reciting, "removing of the sample from the matrix" because it fails to specifically define what elements Applicant is intending to remove or separate, i.e. unbound antibody, unbound EPAMI-hCG, etc.

Claim 15, step b) lacks clear antecedent support in reciting, "the bound matrix".

Claim 15 step b) is indefinite in reciting, "appropriate" because the term "appropriate" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 18 lacks clear antecedent support in reciting, "said antibody" and "the antibody" because a (first) capture antibody, a second capture antibody, and a detecting antibody have been previously recited in this instant claim and claim 14 from which it depends. It is suggested that consistent terminology be used to distinctly define between elements in the claims.

Claim 20 lacks clear antecedent support in reciting, "said antibody" and "the antibody" because a (first) capture antibody, a second capture antibody, a (first)

detecting antibody, and a second detecting label have been previously recited in this instant claim and claim 14 from which it depends. It is suggested that consistent terminology be used to distinctly define between elements in the claims. Same analogous comments for claim 21.

Claim 27 is incomplete for omitting essential elements and method steps, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, it is unclear how the "determining" step is performed in the absence of a label for detection.

In claim 31, preamble, "is" should be --in--.

Claim 31 is indefinite in reciting, "formation of a complex between the antibody and a sample" because it is unclear which component in the sample the antibody is intended to bind.

Claim 39 is indefinite because it unclear what Applicant intends to encompass in reciting, "protein part".

Claim 43 lacks clear antecedent support in reciting, "the monoclonal antibody".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 38-39, and 42-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods relying on monoclonal antibody B152 as the antibody which specifically binds to EPAMI-hCG, does not reasonably provide enablement for any antibody which specifically binds to EPAMI-hCG. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of predicting the likelihood of a negative pregnancy outcome in a female subject using a specific monoclonal antibody that specifically binds an early pregnancy associated molecular isoform of hCG, from here on, EPAMI-hCG.

The state of the prior art- the prior art of record fails to disclose a method of predicting the likelihood of a negative pregnancy outcome in a female subject using an antibody that is specific for and specifically binds an epitope of hCG comprising the EPAMI-hCG.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that any antibody will work to bind the epitope of hCG characterized as the EPAMI-hCG in a method of predicting the likelihood of a negative pregnancy outcome in a female subject

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to use monoclonal antibody B152 which is a monoclonal antibody specific for and specifically binds the epitope of hCG comprising the EPAMI-hCG.

The presence or absence of working examples- there are no working examples that show analogous results for any antibody specific for binding EPAMI-hCG.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of predicting the likelihood of a negative pregnancy outcome in a female subject using any number of antibodies that bind the epitope of hCG comprising the EPAMI-hCG.

The chemical structure of EPAMI-hCG has not been specifically defined or characterized by the specification. General comments on enhanced potency for signal transduction and increased mono- and tri- antennary content of the branched chain sugars with mostly tetrasaccharide instead of disaccharide are insufficient to establish the nature or structure of the EPAMI-hCG. Monoclonal antibody B152 is the only disclosed means for identifying what the specification describes as "unexpected and

previously uncharacterized" isoform of hCG. MAb B152 was generated against a nicked form of hCG isolated from an undefined choriocarcinoma patient and is not specific for nicked isoforms of hCG (while MAb B151 raised against this same antigen is specific for nicked isoforms of hCG).

Recognition of carbohydrate moieties bound by antibodies is a complex and unpredictable task. Unlike linear amino acid epitopes, which can be readily synthesized in vitro and against which other antibodies can be readily made, carbohydrate epitopes are more complex and difficult to synthesize. Knight (Bio/Techniques, January 1989) likens the task to "wrestling with a cloud". She states that "prediction and control of the expression of oligosaccharide remains elusive and threatens to remain for sometime" and the challenge is "a daunting one." According to Knight, "the structure of carbohydrates is much more complex than that of proteins. Dwek also likens the task of sequencing a carbohydrate to "simultaneously sequencing 40-50 proteins". Because carbohydrate structures are a branching series of linked rings, they can combine in many more ways than can linear peptide chains. For comparison, consider that whole three amino acids can combine in only six ways, "three carbohydrate monomers can form over 1,000 different trisaccharide structures" (see page 39, first column, third and fourth full paragraphs). One skilled in the art would reasonably conclude that, even if one has known that B152 epitope comprised carbohydrate moieties, the synthesis of potential carbohydrate moieties would require undue experimentation.

Even if one skilled in the art were able to identify a region of glycosylated hCG or subunit thereof that bound to a particular antibody, Knight teaches the unpredictability of

knowing the exact structure found therein. Knight further states that "on top of this amazing diversity, nature adds what glycobiologists call "microheterogeneity" in the form of discrete subsets- glycoforms- of a glycoprotein. These have different physical and biochemical properties." One skilled in the art would reasonably conclude that these different physical and biochemical properties encompass different epitopes. Knight summarizes that the "demographics of its glycoform populations determine the composite activity of a glycosylated compound. According to Rademacher, Parekh, and Dwek, "any given glycoprotein that consists of different glycoforms will ... have a composite activity, reflecting a weighted average of the activity and incidence of each glycoform" (page 39, third column, second full paragraph). Not only have the glycoforms on hCG not been fully characterized, but neither the glycoisoforms, thereof.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method for any antibody to bind EPAMI-hCG, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work for any antibody other than B152 monoclonal antibody specific for EPAMI-hCG; 3) there is no proper guidance that shows that any antibody that specifically binds hCG would bind the barely characterized EPAMI-hCG to allow predicting negative pregnancy outcome in the instant specification, 4) the nature of the invention is a method of predicting the likelihood of a negative pregnancy outcome in a female subject using a monoclonal antibody specific for and that specifically binds the EPAMI-hCG, 5) the

relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation of a monoclonal antibody that is specific for and specifically binds EPAMI-hCG for use a method of predicting negative pregnancy outcome in a female subject, 4) the nature of the invention is a method of predicting the likelihood of a negative pregnancy outcome in a female subject using a specific monoclonal antibody that specifically EPAMI-hCG, and lastly 7) the claims broadly recite a method of predicting the likelihood of a negative pregnancy outcome in a female subject using any number of antibodies that bind the epitope of hCG comprising the barely characterized EPAMI-hCG.

Given that the nature of B152 epitope was unknown at the time of filing, and the difficulty in making antibodies that recognize on-linear conformational determinants such as carbohydrates, it would require undue experimentation to obtain another antibody which specifically binds to the instant, barely characterized isoform of glycated hCG. Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3, 6, 8, 14-15, 18, 20-21, 27-28, 31-32, 34, 38-39, and 42-43 are provisionally rejected under the judicially created doctrine of double patenting over claims 53, 59-60, 65, 71-72, and 77-82 of copending Application No. 09/017, 976. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of predicting the likelihood of pregnancy outcome by using an antibody, i.e. B152, that specifically binds EPAMI-hCG, quantitating the amount of complex formed therebetween, and correlating the result with temporally matched normal pregnant subjects.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 8, 14-15, 27-28, 31, 34, 38-39, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penfold et al. (US 6,133,048) in view of Morton et al. (WO/ 88/04779, Abstract) and in further view of Sueoka et al. (JP 04300896A).

Penfold et al. disclose an assay method for testing pregnancy status by contacting a urine sample from the subject with a capture antibody which specifically binds human chorionic gonadotropin (hCG) and a detection antibody which specifically binds hCG; thus, in the presence of hCG, a complex is formed in a sandwich format. The capture antibody is an anti-hCG monoclonal antibody immobilized on a latex particle. The detection antibody is an anti-hCG antibody in the device's test line to provide a coloured signal indicative of the presence of hCG (see column 3, lines 22-56 and column 1, line 65 to column 2, line 45). Penfold et al. teach application of the assay with other urinary analytes for determination of pregnancy or relevant fertility status by measuring other analytes including luteneizing hormone, cancer markers, etc.

Penfold et al. differ in failing to disclose specifically using anti-EPF antibodies in a sandwich format to allow detection of early pregnancy in the subject.

Morton et al. disclose using anti-EPF antibodies for detecting the presence of EPF in a sample during pregnancy (see Abstract). Morton et al. disclose that EPF is a protein which is detected from serum or urine throughout the first and second trimesters

of pregnancy and its continuing production is dependent upon the presence and viability of an embryo; thus, a marker for determining outcome of pregnancy. Morton et al. specifically generated monoclonal and polyclonal antibodies for use in the method.

Sueoka et al. disclose that human early pregnancy factor (EPF) can be separated and purified from hCG crude raw powder using dialysis and chromatography. Sueoka et al. specifically uses these methods to obtain a fraction of hCG having EPF activity (see Abstract). According to Sueoka et al., EPF is capable of remarkably early pregnancy fertilization diagnosis. The crude raw powder of hCG is from human villous gonadotropin which comprises the branching processes of the surface of the chorion of developing embryo in mammals that help to form the placenta.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the monoclonal antibodies in the sandwich assay taught by Penfold with the anti-EPF monoclonal antibodies generated by Morton because Sueoka specifically taught that EPF is a remarkable marker for early pregnancy outcome and having generated specific monoclonal antibodies for this specific marker by Morton, a sandwich assay that provides clarity and specificity in detection, not only of pregnancy status itself, but of pregnancy outcome has become possible.

It is proper for purposes of the obviousness rejection to interpret "early pregnancy associated molecular isoform of hCG" as "early pregnancy factor or EPF", in the absence of a definitive and distinctive characterization of this hCG isoform because unpatented claims are given the broadest interpretation consistent with the specification.

7. Claims 6, 18, 20-21, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penfold et al. (US 6,133,048) in view of Morton et al. (WO/ 88/04779) and in further view of Sueoka et al. (JP 04300896A, Abstract), as applied to claims 1-3, 8, 14-15, 27-28, 31, and 38-39 above, and further in view of Birken et al. (Endocrinology, 1993).

Penfold et al., Morton et al., Sueoka et al. have been discussed supra. Penfold et al., Morton et al., Sueoka et al. differ in failing to disclose contacting the EPAMI-hCG with a second capture antibody and a second detection antibody in a sandwich assay.

Birken et al. teach a two-site immunoradiometric assay used to evaluate immunopotency of nicked HcG. Birken et al. teach using a capture antibody that specifically binds INN HcG (intact HcG heterodimer) and a detecting (tracer) antibody that likewise, specifically binds INN HcG. The capture antibody is B109 and the I^{125} radiolabeling antibody is B108. (See page 1391, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to further incorporate monoclonal antibodies in the sandwich assay method taught by Penfold and modified by Morton and Sueoka with the method taught by Birken because Birken specifically taught that use of two-site immunometric assay provides advantage in monitoring complex hCG functions.

Allowable Subject Matter

8. Currently, claim 43 is free of prior art. The prior art of record neither teach or suggest the instant early pregnancy associated molecular isoform of hCG or a characteristic epitope thereof defined by the specific binding of monoclonal antibody B152.

Remarks

7. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

O'Connor et al. (Cancer Research, 1988) teach immunoradiometric assay to evaluate HcG function. O'Connor et al. specifically teach immobilizing capture antibodies into solid phase using B109 which specifically binds INN HcG. O'Connor further teach adding radiolabeled detection antibody, B108, which likewise specifically binds INN HcG. (See page 1362, column 1).

Ellish et al. (Human Reproduction, 1996) teach an immunoradiometric assay which has two solid-phase immobilized capture antibodies and one detection antibody to study early pregnancy loss. Ellish et al. use B109 to capture the INN HcG molecule and B207 to capture HcG free subunit and HcG core fragment. Ellish et al. use B108 as radioactive labeled detection antibody. (See page 4074, column 2).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00

AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-9933. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
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